SHORT COMMUNICATION

Cardio-Oncology: A real need for two correlated specialities

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Cardio oncology is an up-to-date domain and a professional opportunity for new specialists. Literally it is devoted to cardiac care of patients treated with anti-cancer. However, this definition is wider, as similarities between cardio vascular diseases and cancer are significant.

Key Words: *Virus; Vaccination; Treatment; Patients; Hypertensive*

CARDIO-ONCOLOGY – AN OVERVIEW

These two diseases have many things in common.

They are the leading cause of death in the world (1)

They recognize same risk factors: tobacco, lack of exercise, alcohol, familial history, obesity, stress, age. Screening and preventive measures are crucial keys in their treatments: They belong to the 3FOUR50 (2) concept: 3 behaviours –Tobacco, Low Exercise level, Overweight, are involved in FOUR non-communicable chronic diseases: Cancer, Cardio-vascular, Diabetes, Chronic Lower Respiratory Diseases, which are responsive of 50 percent of deaths in the world (including premature). The prevalence of pre-existing heart disease is remarkably high in patient with cancer (3). Some screening measures may over estimate risk and treatment (4-8). Prevention is one of the key not only primary but secondary: exercising, adapted diet, quitting definitely tobacco (9,10) not only decrease cardiovascular but also cancer recurrence, progression (11). Abundant progresses occurred in therapeutics, extended survival and cure, with return to an active life.

Thrombo-embolic events are frequent in both pathologies. End of life cardiac failure has many aspects of patient suffering from terminal cancer (12) Treatment with Monoclonal Antibodies essential in cancer treatment, are now emerging in cardiology (anti PCSK9 as treatment of hypercholesterolemia).

They are chronic, inflammatory diseases with a all life survey and treatment: so Cardiologists keep eyes on MACE (major adverse clinical events) as Oncologists look toward PFS, (Progression Free Survival), OR (Overall Survival).

As the patients get older they may develop heart attack after cancer, vice versa, both diseases and co morbidities may exist at same time. However cardiologists have to be humble regarding oncologists' remarkable efforts.

DETECTING CANCERS

As example, tests to check precancerous state or cancer are better accepted by population (13). Regular, colon, cervical, breast cancer screenings are effective. Vaccination against human papilloma virus in young girls (and boys) is gone to be accepted as prevention for cervical cancer.

Cardiologists have also evidence based guidelines for prevention and treatment with convincing trials but treating asymptomatic people is a wager. High risk patients accept screening tests but adherence is a real challenge.

Acceptance: Yes

Adherence: No (i.e., statin treatment).

Asymptomatic patients accept the treatment and survey of their cancer (subject with BRCA 2 mutation). Genetic testing is innovative and growing up in oncology care (14).

Displaying of specific receptors and enzymatic mutations (immunohistochemistry) of cancerous cells, this last decade, opened the doors-beside classical chemotherapy- for target therapy.

Biologic therapy, immunotherapy, check point inhibition of signalling pathways and hormonotherapy

Oncologists are more and more concerned in treating cell specificity rather organ cancer. People acceptation of cancer drugs and their side effects has no common measures with our cardiac drugs. Only half of patients who suffered from myocardial infarct continue after one year to take this low cost high efficient, Aspirin. Same for anti-hypertensive and anti- cholesterol effects (15).

Cardiologists and their patients

Cardiologists' task is sometimes easier, suffering from a heart attack or heart failure does not provoke the same fear than suffering from cancer. Except for stroke, cardio vascular diseases are considered as in the order of things. Chronic pain, permanent disability, bulky weakness is not in people's register of cardiac events. We have no "Announcement Consultation" After coronary stent procedure or an episode of acute cardiac failure patients consider they are definitely cured, forgot usual care and follow up. Sudden cardiac death is a remote and accepted possibility. On the opposite chronicity, anguish, depressions are within the diagnostic of cancer. This may be one explanation for patients' compliance in cancer treatment. Of note the rapidity in institutions' acceptance for-the costly-therapeutic use before full trials results and long term effects in both sides –efficiency/safety (16).

Cardiac consequences of cancer and hematologic treatments

Cardio-oncology devoted to cardiac care in patients suffering from cancer. Impairment of cardiovascular system is the One where oncologists, haematologists and cardiologists must be involved. Nearly all oncologic medications are related in one or more heart disorders. Everyone knows the hematologic, renal, digestive, hair, skin... side effects dramatic but transient seen in the oncologists' field. Regarding cardio vascular it is more than side effects but aggression with sometimes irreversible damages (17). Every part of cardio vascular system can be affected. Furthermore, involvements may be acute, chronic, insidious, and irreversible. Forty years ago cardiovascular damage was not considered as an important problem. The goal was at that time to slow down the cancer and for lymphoma or hematologic related situations, to cure. Overall survival, progress free survivals were counted in months sometimes in weeks. Young people cured from hematologic cancer in 60's or 70's were the first witnesses 40 years later of harmful effects of radiotherapy and chemotherapy (18).

CARDIO-ONCOLOGY IS CRUCIAL

Intense successes in cancer treatment changed the opinion on the patient's future health. Thanks to research, more and more patients are cured or have a long survival after hematologic or tumour cancer. Cardio vascular diseases may emerge related to oncologic treatment but also as a consequence of age, obstinate smoking... Population age is increasing, so patients with cancer may have past history of high blood pressure, coronary artery disease, cardiac failure, thrombo embolic events. Co morbidities well known by cardiologists emerge in patients having cancer and will interfere with cancer therapy.

Selected oncologic treatments for selected cancer in selected patients are

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corner stone and reason of cardio-oncology. Both specialists are now defied with a colossal challenge, protect the heart and cure cancer. This is cardio oncology speciality ambition! We are faced more and with patients suffering of both heart disease and cancer. What drug we can choose? Is there any alternative? This Oncologists and Cardiologist dilemma was the motivation of Cardio Oncology Speciality. The cardio Oncology Society was heralded in 2010 (19) following the initiative of US and Italian cardiologists.

The first European Cardio Oncology department was created in Milano (Italy) the interests of such specific area is to have patient's centered decision, qualified specialists quickly available, permitting exchange opinions, treatment options. Present in the place a specific panel of echocardiography, nuclear medicine specialists, specific nurses' staff with a personalized contact and material.

CARDIAC EFFECTS OF CANCER THERAPIES

Radiotherapy

Radiotherapy was beside surgery, and later chemotherapy, the first efficient treatment of solid and hematopoietic cancers. High doses of chest and total body radiotherapy were used in sixties and next decade. Combined with chemotherapy notably Anthracyclines patients suffering from Lymphoma (20), breast cancer were successfully cured (21). However some 20, 30 years later cardiac side effects of these necessary but harmful therapies appeared. Constrictive pericarditis, cardiac failure, coronary (and carotid) symptomatic stenosis, cardiac valve impairment, appeared. The cumulative effect of high dose therapy and association to chemotherapy, the effect of aging are now well known. Targeted doses after a very fine definition of tumor contours are now the rules. The patient has also to play a role in this situation, controlling the cardiac risk factors, at pole position, stop tobacco. Patients treated and cured in 70's for breast cancer, lymphoma, have left the oncologic area and progressively develop neglected cardiac symptoms. Radiotherapy is an old souvenir and so the protocol doses. If fortunately patients left the oncologic field, they were not in cardiologic one. Cardio oncology clinics will overcome this failure. At last, aware of this requirement, The European Cardiology Congress in Roma 2016 finally edited specific Cardio Oncology Guidelines (21-23) Patient's follow-up treated by chest radiotherapy include "Every 5 year systematic cardiac and vessel clinical and ultra-sonographic check, in high risk (cardiovascular) patient, every 10 years otherwise"

Chemotherapy and cardiovascular side effects

Myocardium: If all anticancer medication may be harmful for the heart and vessels, the leaders belong to the Anthracyclin class (24,25)

Conventional chemotherapy

Anthracycline. Adriamycin (or Doxorubicin) is the foremost drug in this section. It is one of the oldest and more efficient used in treatment of many solid and hematologic cancers. Toxicity can be acute or torpid, self-evolving after months. Strong recommendations and contraindication are now erected. Ejection fraction of the left ventricle has to be previously and regularly evaluated (not only 2D echocardiography but myocardial strain and tissue imaging- speckle tracking echocardiography). An echocardiography is done every 3 months or in case of cardiac toxicity before each protocol. The admitted borderline of Ejection Fraction is 50%. With titrated doses, low speed infusion, acute cardiac toxicity is rare, and established in concert with cardiologists, results of echography it is now possible to preserve future cardiac function. This is a real dilemma for cardiologists and oncologists when cardiac markers are not suitable. Should we continue with the previously scheduled doses to definitely eradicate the cancer but make irreversible damage to the heart? Or stop the cardio-toxic product to avoid future cardiac failure? Preventive treatment with Cardioxane (23) is partially efficient but this drug may have cardiac toxicity. Beta-blockers, Converting Enzyme Inhibitors must be used with overt myocardial dysfunction or cardiac failure (26) However levels of recommendations are still weak in primary prevention. Other conventional chemotherapies may affect directly or indirectly myocardial function via myocardial ischemia, conceivably reversible (22).

Alkylating agents: Cyclophosphamide (Myocarditis, pericarditis)

Antimetabolites: Fluorouracil, Capecitabine (coronary arteries spasm)

Anti-microtubule agents: Vinca alkaloids (coronary artery spasm)

Targeted therapy

Monoclonal antibodies: The understanding of molecular pathways involved in tumour progression heralded two decades ago the emergence of specific blockage of cancer cells metabolism. Interfering with kinase receptor (monoclonal antibodies) or binding directly with its substrate (small molecule inhibitors) As a consequence of tyrosine kinases crucial, wide spread role, myocardial, as other normal cells, are affected by this specific molecular action. Of note targeted treatment is a relatively recent one, it is difficult to evaluate the long term cardiovascular consequences and the role of associated anti-cancer therapies Human Epidermal Grow Factor Receptor 2 (HER-2) Inhibitor.

Trastuzumab and Pertuzumab are monoclonal antibodies which block cell surface protein HER-2, over expressed in some tumours notably breast cancer. HER-2 receptors are present on myocardial cells explaining the possible cardiac damage. However progression to definitive myocardial dysfunction can be anticipated. Regular echographies and biological markers evaluation are the keys to prevent or reverse damage as titrated doses of drug association (Anthracycline, Paclitaxel) (27,28).

Signalling pathway inhibition

Vascular Endothelial Grow Factor Receptor (VEGFR) inhibition

Cardiac and vascular dysfunctions are frequent with angiogenesis inhibitors. The antinomy of impairing vessels development, endothelial function, in tumour and cardiovascular cells is a dilemma between cardiologists and oncologists. Monoclonal antibodies Bevacizumab, Ramucirumab interfering with cell receptors, like small molecule Tyrosine Kinase Inhibitors (Sunitinib, Sorafenib), involved in VEGFA function, are responsible of cardiomyopathy, hypertension and thrombo embolic events (29,30). Some studies report similarities between toxic effects of VEGFA R inhibitors and preeclampsia features (31). Follow up of patients suffering from vascular events during anti VEGF have to be monitored via a multidisciplinary approach and long term follow-up.

Vessels: Arterial spasm, arterial and venous thrombosis

As we describe high blood pressure is anti VEGF receptor common harm. But coronary and peripheral arteries may be affected by multi targeted tyrosine kinase inhibitors. We have to pay attention toward coronary arteries: double-triple-burden myocardial damage: myocardial consequence due to anthracyclines, radiotherapy stenosis plus myocardial fibrosis and coronary spasm. Coronary, cerebral and peripheral vascular events are described with Dasatinb, Nilotinb, Ponatinb. Monitoring peripheral arteries via Ankle Brachial Index should be mentioned (22) of note small molecule tyrosine kinase inhibitors may affect cholesterol levels.

Venous thrombosis is frequent in patients suffering from cancer. Inflammations, specific hematopoietic cancers, low level of exercise, underlying cardio vascular disease are well recognized comorbidities (32) Immunomodulator Lenalidomide a potent drug used in myeloma is involved in thrombo embolic complication as myeloma itself (33).

Pulmonary hypertension

Pulmonary arterial hypertension is a potential complication of solid tumours or hematologic cancer therapies (stem cell bone marrow transplantation). Tyrosine Kinase Inhibitor, dasatinb used in leukaemia can induce precapillary pulmonary hypertension eventually reversible after drug removal.

Alkylating agents and Cyclophosphamide may contribute to the development of Pulmonary Arterial Hypertension (22,23).

Chronic thromboembolic pulmonary hypertension is a frequent situation pointing to the importance of anticoagulant treatment (34,35).

Cardio-Oncology specialists (including Haematologists) are at corner stone of follow-up: risk benefits ratio cancer vs PAH. Regular assessment (Echocardiography for Pulmonary pressures, right ventricular overload, Left Ventricular Function) is essential.

Immunotherapy

Important progress in target therapy came from drugs dedicated to enhancement of immunity system. Blockage of PD 1 receptor, a mutation seen in melanoma and pulmonary cancer, by monoclonal anti-body Nivolumab permitted improvement in Overall and Progression Free Survival. Inhibition of T cells PD 1-L (Imulimab) is also a potent therapiy in these situations. If immunotherapy has not specific toxicity on myocardial cells, high doses or association of these drugs can lead to immune myocarditis and lethal consequences (36). Amplifying immune system as known consequences on pulmonary, digestive, skin, rheumatology, renal and endocrine systems and myocardium.

Multitargeted tyrosine kinase inhibitors

Immunomodulators: Small molecules inhibitors, specific or multitargeted Tyrosine Kinase Inhibitors now and in the next future play an important role they do not seem to affect heart. However long term consequences are not known, precise cardiovascular follow-up is mandatory.

Essential Cardio Oncology specialists' assessments

Multitargeted Imatinib is a potent medication in chronic myeloid leukaemia, without significant cardiovascular harm since introduction in 2000 (37). However the recent generation (danatinib, ponatinib) is involved in cardiovascular toxicity, cardiac, cerebral and peripheral ischemic complications (38).

Thromboembolic frequently seen in cancer

It is sometime difficult to point medication but disease. Anti-Tumour Necrosis Factor (TNF) Lenalidomid used in Myeloma (33) may require therapeutic doses anti-coagulation. Thrombopenia, part of the disease or induced by therapy may cause problem. Thrombo embolic events necessitate heparin (low weight molecular heparin if renal function permits) during the first 3 months. As anti-vitamin K may initiate cascade of procoagulant proteins, will not be used. Special attention is also required concerning drug interference with antivitamin K. New Direct Oral Anticoagulants have not been studied (22)

Arrhythmic problems

Check point inhibitors, Proteasomes inhibitors, anti PD 1 and PD 1 Ligant, Tyrosine Kinase Inhibitors (Sunitinib) may also affect nodal network (39).

Atrial Fibrillation paroxysmal or permanent, QT interval lengthening are side effects of Inhibitors of Signalling Pathways. Atrio-ventricular conduction can also be affected by Tyrosine Kinase Inhibitor, Myocardial function by Everolimus an inhibitor of EGFR (Epidermal Growing Factor Receptor) Stopping these very successful therapies because of heart rate disturbances is infrequent (22). If lethal ventricular arrhythmias arising from lengthening of QT interval with tyrosine kinase, arsenic, platinum are rare, initial evaluation of the EKG, regular follow-up, avoiding class III or Ic anti-arrhythmics may be necessary. Regular blood tests permit correction of ionic abnormalities. Of concern are underlying ischemic cardiopathy, kidney failure as frequent comorbidities. A cardiac pace maker is sometimes needed as atrio-ventricular bloc can be complication of chest radiotherapy (22). Some medications should be avoided which is not always easy, anti-emetics, anxiolytics, specific serotonin recapting Inhibitors...calcium channel dihydropyridine class, which interfere with Glycoprotein P may potentiate toxic effect of Tyrosine Kinase inhibitors (22).

Special populations

Once again Cardio Oncologists are in the core of discussions with their colleagues specialists**.**

Paediatric cancer population

Hematologic and tumour cancer in children represent a vast challenge. Not only because of the seriousness of the situation but the titration of the different therapeutic option for now, and future Quality Of Life. Patients who suffered from a cancer in their childhood pay a heavy contribute for having another cancer and develop cardiac failure during their adulthood. Treatment Innovation and clear-cut radiotherapy do not exclude a specific cardiac follow-up (40,41).

Pregnant women

The way to conduct the cancer treatment in this situation comes from consensus. No scientific data about the maternal drug cardiotoxicity. Drug cardiotoxicity according to experts' opinions is not overwhelmed in pregnancy.

There is no definitive information about placenta transfer of anticancer medications and the foetus' risk is not known. Obstetricians, paediatricians, cardio-oncologists' shared opinions are mandatory in this alarming situation, informing as best as possible the patient and her family. (22,42-44).

CARDIOVASCULAR TREATMENT AND CANCER RISK

Statins are regularly sued for many side effects. Some studies pointed the hypothetical development of pancreatic cancer. Recently researchers discovered a cholesterol metabolite which activates the oestrogen receptor and may stimulate breast cancer tumour (45).

Lowering cholesterol through lifestyle and medication may reduce risk or slow down progression of abnormal cells

Preventive measures and treatment

Assessing initial cardio vascular risk is an important step before initiating anti-cancer therapeutics. Stopping tobacco, controlling high blood pressure, claiming on physical activity, even light, as soon as possible are corner stones in both specialities and part of the future well-being. Participation in social events fight against depression should not be neglected.

Cardiac evaluation in medium or high risk patients is mandatory

Tailored treatment: Radiotherapy, conventional chemotherapy, target anti-cancer drugs frequent discussions between patients, attending physician, oncologists, cardiologists permit now to admit the obligatory dilemma, diminishing the patients (and doctors) anxiety. Special precaution with young people, to patients who underwent previous radiotherapy, to anticancer and cardiovascular drugs association.

Medications can also counterbalance cardiac harms; studies are in the fields of research.

Dexrazoxane (22) is effective in prevention of anthracyclines toxicity. It has a restricted agreement due to his potential inhibition of anthracyclines, possibility of future cancer.

Beta-blocker (Carvedilol...) Angiotensin-converting enzyme inhibitors and angiotensin receptors blockers are potential medications according to well-developed and continuing trials. On-going studies with Statins and their pleiotropic effects such as anti-inflammatory, Aldosterone antagonists due to their anti-fibrosis impact.

Major difficulties are the lack of definite specific markers pointing early stage of myocardial dysfunction. Association of ultrasonography and biologic tests (cardiac enzyme, BNP, kidney, liver functions) may help, waiting for conclusive data with magnetic resonance imaging. Scientific Societies recommendations are still with consensual.

The special relationship between cardio-vascular and cancer

New anticancer treatments affect other organs, notably immunotherapy, but to my knowledge there in no need for Nephro-oncology society, no more about Pulmo-oncology etc. There is something special between cardiovascular and cancer a complex association which can be caused by similar underlying mechanisms, risk factors inflammatory situation. Controlling diet, fighting obesity, banning tobacco, alcohol, practising regular exercises prevent both diseases occurrence and recurrence (3,46,47).

CONCLUSION

Treating Not Threating

In spite of noticeable progress in cardiac care during, and after anticancer treatment important challenges devoted to cardio oncology remain predisposing factors toward left ventricular failure and its transition to overt cardiac insufficiency. Define cardiac monitoring approach. Cardiac outcomes after cancer therapies, focused on Quality of Life (22).

Cardio Oncologists have also to work with pharmaceutical companies on the way to innovative therapy, cardiovascular safety. Not overlooking costs (48), post marketing alerts expressly for accelerated approval. These approaches are just around the corner (49).

It took 7 years from International Cardio-oncology Society (Milano) to ESC Pocket Guidelines "Cardio Oncology" published in 2016 ESC Congress in Roma. 7 years to from Milano to Roma 600km distance, not a so long way.

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